Limitation of enzymatic models for predicting myocardial infarct size

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SUMMARY The possibility of predicting myocardial infarct size from early enzyme measurements was studied using a physiological two compartment distribution model. Based on this the time dependent appearance function in plasma was calculated for creatine kinase, aspartate aminotransferase, and lactate dehydrogenase in 29 patients suffering from acute myocardial infarction. On average, the appearance function of the three enzymes started four hours after the onset of symptoms, and the maximum was reached after 12 hours for creatine kinase, 13 hours for aspartate aminotransferase, and 22 hours for lactate dehydrogenase. The cumulated appearance function was used as an acceptable estimate of infarct size. The prediction of infarct size from defined points of the appearance function curve for each of the three enzymes was attempted according to a set schedule during the first 25 hours after the onset of myocardial infarction. The prediction using creatine kinase was superior to the other enzymes. Even so, a reliable prediction could only be established at the very earliest from nine hours and this is too late, as irreversible loss of myocardium occurs rapidly after the onset of symptoms. This, together with the fact that other models have unacceptable variability of the prediction, lead to the conclusion that enzymatic predictive models are of no practical value in clinical intervention studies to reduce infarct size.

Controlled clinical trials designed to evaluate the influence of pharmacological agents on myocardial infarct size can be carried out either after randomised allocation of patients to two or several groups, or the patients can be used as their own controls. Should the first principle be employed a large number of patients is necessary in each group, requiring in actual practice multicentre trials, because of the pronounced interpatient variability of the evolution and size of the infarction.[1]

Alternatively, the patient may be used as his own control, which in theory would reduce the number of patients required in clinical investigations. This has been used in various ways, and one is the method of prediction,[2 3] the principle of which is prediction of infarct size from very early changes in an indicator of myocardial damage. A prerequisite is that the prediction can be achieved so early that the modified and the predicted infarct size can be compared in the individual patient. Shell and collaborators[2] suggested a one compartment predictive enzymatic model requiring the collection of plasma enzyme values during the first seven hours. This model has been the object of criticism because it is an oversimplification of a highly complex biological system and because of the effects of the great variation in the model variables.[4–8]

Recently we have devised a new more physiological two compartment distribution model[9] which forms the basis for the calculation of the appearance function for the enzymes: creatine kinase (CK), aspartate aminotransferase (AST), and lactate dehydrogenase (LD). Using this model the object of the present study has been to determine how early after the onset of infarction it is possible to obtain a reliable prediction of infarct size.

Patients and methods

The investigation included 29 patients with acute myocardial infarction admitted to the coronary care unit on average 112 minutes (range 25 to 280 min) after the onset of retrosternal pain of more than 20 minutes duration. This and daily routine recordings of a 12 lead electrocardiogram and a diagnostic rise in the daily determination of serum enzymes (CK, AST, and LD) were used in establishing a definite diagnosis of acute myocardial infarction.[10] The average age of

the patients was 63 years (range 44 to 80); 20 men and nine women. They were treated according to the usual procedure, that is rest in bed, morphine, antiarrhythmic drugs, diuretics as required, and oxygen via a nasal catheter when necessary.

Blood for measurement of total CK, total AST, and total LD was sampled on admission and every three to four hours throughout 48 hours, and then three to four times daily for approximately one week.[8] Catalytic activity in plasma of CK (EC 2.7.3.2), AST (EC 2.6.1.1), and LD (EC 1.1.1.27) was determined according to the Nordic recommended methods.[11][12]

The calculation of the appearance function, which is the time dependent influx of new enzymes into plasma, was based on a two compartment model (Fig. 1). The appearance function was calculated for each time interval between two consecutive blood samples by simultaneous solution of mathematical equations for the differential changes in amount of enzyme in plasma and extravascular space, respectively, and the values of exchange rate constants for enzymes between the compartments were chosen from rate constants for proteins with molecular weights similar to those of the three enzymes.[9] Based on this, plasma enzyme activities were transformed to enzyme appearance function without assumptions as to the shape of these curves (that is no curve fitting technique is applied). The characteristics of the appearance function curve are shown in Fig. 2. The 10% level of the maximum of the appearance function is depicted on the curve. This is used as an estimation of the biological background noise of the enzymes. The cumulated appearance function (not shown in Fig. 2) is used as an index of infarct size.

STATISTICAL ANALYSIS

Differences between groups and times were evaluated using a two way analysis of variance. Additional differences in times were evaluated by means of an
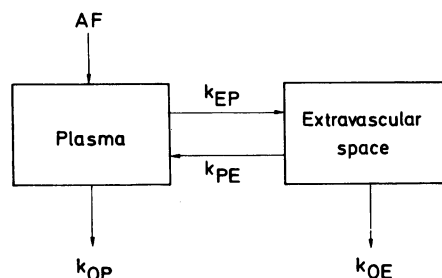
Fig. 2 *Characteristics of appearance function for enzymes in plasma according to a two compartment model. The maximum of the appearance function (AF_{max}) and its occurrence from onset of chest pain (AF_{t-max}) are shown. The start and the end of the appearance function ($AF_{t-start}$ and AF_{t-end}) are the times at which the appearance function exceeds or goes below, respectively, the level of 10% of the maximum of the appearance function ($AF_{max}/10$). The period of appearance (AT) is the difference between the end and the start of the appearance function ($AF_{t-end}-AF_{t-start}$). Finally, defined point of the appearance function (AF_{def}) and time for its occurrence (AF_{t-def}) are shown on the curve.*

unpaired t test. Analysis of correlation was used for calculation of the coefficient of correlation (r) and coefficient of determination (r^2). Comparison of r values was performed using Fisher's z-transformation of r.[13] A significance level of 0·05 was selected.

Results

Table 1 shows the characteristic times of the appearance function for CK, AST, and LD. The start of the appearance function occurred, on average, four hours after the onset of symptoms and there was no significant difference between the three enzymes.

The maximum of the appearance function occurred, on average, after 12 hours for CK, after 13 hours for AST, and after 22 hours for LD; these were significantly different. This difference was due to LD, as there was no significant difference between CK and AST. Similarly, the period of appearance of the three enzymes showed a significant difference, again because of LD.

The cumulated appearance function of the three enzymes was mutually correlated, as shown in Table 2.

Fig. 1 *The two compartment model for the turnover of enzymes between plasma and extravascular space. AF, appearance function, k_{EP} and k_{PE}, rate constants for exchange of enzymes between the two compartments. k_{OP} and k_{OE}, rate constants for katabolism in plasma and extravascular space, respectively.*
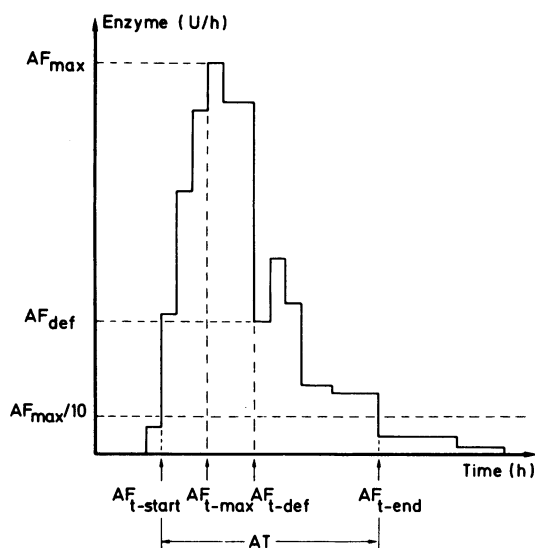
Table 1   *Characteristic times (mean and range in hours) of appearance function of enzymes in plasma in acute myocardial infarction*
(n=29)

	Start of appearance function* (h)		Maximum of appearance function* (h)		Period of appearance* (h)	
	Mean	Range	Mean	Range	Mean	Range
CK	4·0	1·5– 9	12	2·0–24	33	11– 74
AST	3·6	1·5–10	13	2·0–35	36	11– 79
LD	3·8	1·2–14	22	4·9–42	45	11–134

*For definitions see legend to Fig. 2.

Table 2   *Interrelation of cumulated appearance functions of CK, AST, and LD (n=29)*

Enzyme correlation	Cumulated appearance function	
	r	p
CK and AST	0·92	<0·001
CK and LD	0·81	<0·001
AST and LD	0·83	<0·001

Table 3   *Coefficient of correlation between maximum and cumulated appearance function for CK, AST, and LD (r), as well as coefficient of determination (r²) (n=29)*

Enzyme	r	p	r²
CK	0·87	<0·001	0·76
AST	0·77	<0·001	0·59
LD	0·63	<0·001	0·40

The three r values (0·92, 0·81, 0·83) were not significantly different.

As expected, the maximum of the appearance function of all three enzymes was significantly positively correlated to the respective cumulated appearance function, as shown in Table 3. The coefficients of determination, however, were rather low in respect of AST ($r^2 = 0·59$) and LD ($r^2 = 0·40$).

In order to predict the cumulated appearance function during the early phase of myocardial infarction

various defined points of the appearance function curve were correlated to the respective cumulated appearance function during the first 25 hours after the onset of symptoms; Fig. 3 shows these r values plotted as a function of time, as well as the r values between the maximum and cumulated appearance function for all three enzymes.

In respect of CK, a comparison of r values between the maximum and cumulated appearance function (r=0·87) and between defined points and cumulated
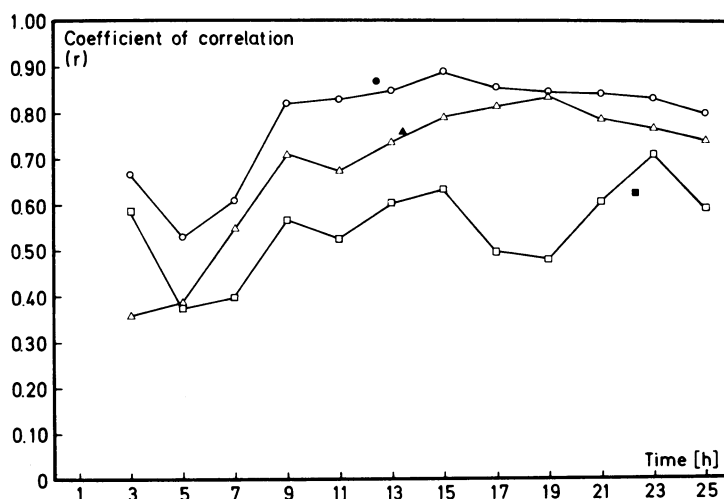

Fig. 3   *Correlation coefficients between defined points of the appearance function curve and the cumulated appearance function as well as between the maximum and cumulated appearance function for CK, AST, and LD, plotted as a function of time. Open circles, open triangles, and open squares =r values between defined points and cumulated appearance function for CK, AST, and LD, respectively. Filled circle, filled triangle, and filled square =r values between maximum and cumulated appearance function for CK, AST, and LD, respectively.*

appearance function showed that the latter values were significantly lower at times three, five, and seven hours, whereas there was no significant difference within hours nine to 25.

At all times the r values for CK were higher than the corresponding values for the other two enzymes; a significant difference could be shown between CK and LD (p<0·05).

Discussion

The size of an acute myocardial infarction has been estimated from plasma time-activity curves using models attributing serial changes in plasma enzyme activity to release from the heart and concomitant disappearance from the circulation.[14-18] These models are, in principle, based on the assumption of a one compartment distribution space; criticism, however, has been raised against these as they are very sensitive to variations in the variables used and simplify an extremely elaborate system.[4 5 8] As several proteins, including enzymes, are present in both extravascular and intravascular pools it has been suggested that multicompartment models should be used, which, from a physiological point of view, should provide a more valid evaluation of the extent of enzyme release from infarcted heart muscle.[9 19 20] It has been pointed out, however, that for the purpose of calculation, a number of extravascular spaces may be lumped together into a single extravascular compartment.[21] Thus, a two compartment model is preferable to a one compartment model for describing the distribution of enzymes.[9]

Our results indicate that the leakage of enzymes from heart cells starts early after the infarction. Thus, the time dependent influx of new enzymes into plasma took place in some patients a little more than one hour after the onset of symptoms, and, on average, after four hours for the enzymes investigated in this study. Probably because of an increase in cell membrane permeability,[19] the appearance rate rises progressively and reaches a maximum, on average, after 12 hours for CK, after 13 hours for AST, and 22 hours for LD.

When using the cumulated appearance function as an estimate of infarct size, the present study shows that the three enzymes are equally applicable. This is based on the fact that there was no significant difference between the coefficients of correlation of the cumulated appearance functions when studying the interrelation of CK, AST, and LD.

It has been suggested that the maximum activity of enzymes in plasma gives a reasonably good clinical estimate of infarct size[7 8] because there is a close correlation between maximum CK values and calculated infarct size, both in a one compartment and a two compartment model (r=0·93 and 0·91, respec-

tively).[8 22] We have also found a high coefficient of correlation (r=0·87) between the maximum of the appearance function and the calculated infarct size in respect of CK. The corresponding correlation of AST and LD were poorer and in our opinion unacceptable as the coefficients of determination (r^2) were only 0·59 and 0·4, respectively. This means that a variation of the maximum appearance function can explain 59% of the variation of the calculated infarct size when using AST and 40% in the case of LD. The observation that the maximum of the appearance function of CK is a good estimator of infarct size can be used in clinical trials with between-patient study design.

The feasibility of predicting infarct size from plasma enzyme activities in the very early phase of myocardial infarction has attracted considerable interest. In 1973, Shell and coworkers designed a curve fitting technique for this purpose and used data obtained during the first hours after the initial CK rise to predict the most likely course of the entire curve. In order to estimate the expected infarct size, both the predicted and observed values were analysed using the same one compartment model.[2] Various modifications and improvements have been suggested in the original predictive algorithm,[17 18 23] but none has been able to overcome the main objection, that even small "noise" in the collected data results in such variability in predicted infarct size that the usefulness of the method has been seriously questioned.[4-7]

Infarct size can be estimated and consequently predicted with reasonable reliability when the maximum appearance rate of CK occurs, that is, at 12 hours. Irreversible loss of myocardium, however, takes place so rapidly after onset of symptoms that intervention must be carried out during the first four to six hours[24 25] in order to have the greatest beneficial effect. Thus, it is obvious that prediction must be performed even earlier, and the time for maximum appearance function of CK is too late in this respect. Therefore, predictors appearing earlier than the maximum appearance function and having the same validity have been sought in the present investigation. This has shown that reliable prediction can only be established from nine hours despite the use of a more physiological two compartment distribution model.

In general, these findings clearly show that enzymatic predictive models for infarct sizing are too unreliable and cannot be used early enough after the onset of infarction for the patient to act as his own control in clinical intervention studies.

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